FORM PTO-1390 (REV 5-93)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY DOCKET NO. 108907-00016
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		DATE: July 17, 2001
		U.S. APPLN. NO. (IF KNOWN, SEE 37 C.F.R. 1.5) 09/868932

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/00353	18 January 2000	26 January 1999

TITLE OF INVENTION: SYNTHESIS METHOD OF NITROXYMETHYLPHENYL ESTERS OF ASPIRIN DERIVATIVES

APPLICANT(S) FOR DO/EO/US: Piero DEL SOLDATO (Milano, Italy); and Michele GARUFI (Milano, Italy)

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371. (THE BASIC FILING FEE IS ATTACHED)

2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. ☒ This express request to begin national examination procedures [35 U.S.C. 371(f)] at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. ☒ A proper demand for International Preliminary Amendment was made by the 19th month from the earliest claimed priority date.

5. ☒ A copy of the International Application as filed [35 U.S.C. 371(c)(2)]
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).

6. ☒ A translation of the International Application into English [35 U.S.C. 371(c)(2)].

7. ☐ Amendments to the claims of the International Application under PCT Article 19 [35 U.S.C. 371(c)(3)]
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.

8. ☐ A translation of the amendments to the claims under PCT Article 19 [35 U.S.C. 371(c)(3)].

9. ☒ An oath or declaration of the inventor(s) [35 U.S.C. 371(c)(4)].

10. ☒ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 [35 U.S.C. 371(c)(5)].

Items 11 - 16 below concern other document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98.

12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. 3.28 and 3.31 is included.

13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☐ A substitute specification.

15. ☐ A change of power of attorney and/or address letter.

16. ☒ Other items or information: CHECK NO. 321914; Form PCT/ISA/210; Form PCT/IPEA/416; Form PCT/IPEA/409

U.S. APPLN. NO. (IF KNOWN SEE 37 C.F.R. 1.5(b)) 09/868932	INTERNATIONAL APPLICATION NO. PCT/EP00/00353	ATTORNEY DOCKET NO. 108907-00016 DATE: July 17, 2001

17. ☒ The following fees are submitted:

Basic National Fee [37 C.F.R. 1.492(a)(1)-(5)]:

Search Report has been prepared by the EPO or JPO.....$860.00
International preliminary examination fee paid to USPTO
(37 C.F.R. 1.482).....$690.00
No international preliminary examination fee paid to USPTO
(37 C.F.R. 1.482) but international search fee paid to USPTO
[37 C.F.R. 1.445(a)(2)].....$710.00
Neither international preliminary examination fee
(37 C.F.R. 1.482) or international search fee
[37 C.F.R. 1.445(a)(2)] paid to USPTO.....$1,000.00
International preliminary examination fee paid to USPTO
(37 C.F.R. 1.482) and all claims satisfied provisions of
PCT Article 33(2)-(4).....$ 100.00

	CALCULATIONS	PTO USE ONLY
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860.00	
Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date [37 C.F.R. 1.492(e)].		

Claims	Number Filed	Number Extra	Rate		
Total Claims	5 - 20 =	0	X $ 18.00		
Independent Claims	1 - 3 =	0	X $ 80.00		
Multiple dependent claim(s) (if applicable)			+ $270.00		

TOTAL OF ABOVE CALCULATIONS =	$ 860.00	
Reduction by one-half for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 C.F.R. 1.9, 1.27, 1.28). -		
SUBTOTAL =	$ 860.00	
Processing fee of $130.00 for furnishing the English translation later the ☐ 20 ☐ 30 months from the earliest claimed priority date [37 C.F.R. 1.492(f)]. +		
TOTAL NATIONAL FEE =	$ 860.00	
Fee for recording the enclosed assignment [37 C.F.R. 1.21(h)]. The assignment must be accompanied by an appropriate cover sheet (37 C.F.R. 3.28, 3.31). $40.00 per property +	$ 40.00	
TOTAL FEES ENCLOSED =	$ 900.00	
	Amount to be refunded	$
	Charged	$

a. ☒ A check in the amount of $900.00 to cover the above fees is enclosed.
b. ☐ Please charge my Deposit Account No. 01-2300 in the amount of $ to cover the above fee.
A duplicate copy of this sheet is enclosed.
c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 01-2300.

NOTE: Where an appropriate time limit under 37 C.F.R. 1.494 or 1.495 has not been met, a petition to revive [37 C.F.R. 1.137(a) or (b)] must be filed and granted to restore the application to pending status.

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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:

DEL SOLDATO et al

International Appln. No.: PCT/EP00/00353

Filed: Concurrently herewith Attorney Dkt. No.: 108907-00016

For: SYNTHESIS METHOD OF NITROXYMETHYLPHENYL ESTERS OF ASPIRIN DERIVATIVES

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231 July 17, 2001

Sir:

Prior to calculation of the filing fees and initial examination of the application, please amend the above-identified application as follows:

IN THE CLAIMS:

Please amend claim 4 as follows. A copy of the marked up original claims is attached to this response showing the changes as set forth in amended 37 CFR 1.121.

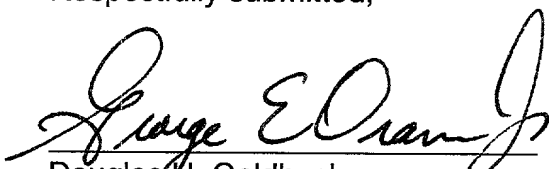
4. (Amended) A process according to claim 1, wherein the aspirin derivative of formula R-COOH is the acetylsalicylic acid.

REMARKS

Claims 1-5 are pending in this application. By this Amendment, claim 4 is amended to correct the multiple dependency thereof and to place this application into better condition for examination. No new matter has been added.

In the event that there are any fees due with respect to the filing of this paper, please charge Deposit Account No. 01-2300.

Respectfully submitted,



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DHG:scc

Enclosure: Marked-up Copy of Amended Claim 4

MARKED-UP COPY OF AMENDED CLAIM 4
INTERNATIONAL APPLN. NO. PCT/EP00/00353
Our Ref: 108907-00016

4. (Amended) A process according to [claims 1-3] claim 1, wherein the aspirin derivative of formula R-COOH is the acetylsalicylic acid.

SYNTHESIS METHOD OF NITROXYMETHYLPHENYL ESTERS OF ASPIRIN DERIVATIVES

* * * * * *

The present invention relates to an improved synthesis for obtaining (nitroxymethyl)phenyl esters of aspirin derivatives.

These esters have interesting pharmacological and therapeutical properties; specifically they show an improved systemic and local tolerability, at the level of the gastric mucosa (WO 95/030641) and they are more effective as antithrombotic medicines (WO 97/16405).

It is known in the prior art that the (nitroxymethyl)phenyl esters of the aspirin derivatives are prepared by reacting (nitroxymethyl)phenol with the aspirin derivative in the acid form (WO 97/16405).

In particular the preparation of (nitroxymethyl)phenol is carried out starting from (hydroxymethyl)phenol through the following steps:

- reaction of phenol with HBr in an organic solvent to obtain (bromomethyl)phenol;
- reaction of (bromomethyl)phenol in an organic solvent with $AgNO_3$ to form (nitroxymethyl)phenol.

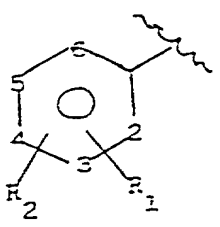
The synthesis of the (nitroxymethyl)phenol intermediate has the following drawbacks. The (bromomethyl)phenol is a chemically unstable and irritant compound. The nitroxy

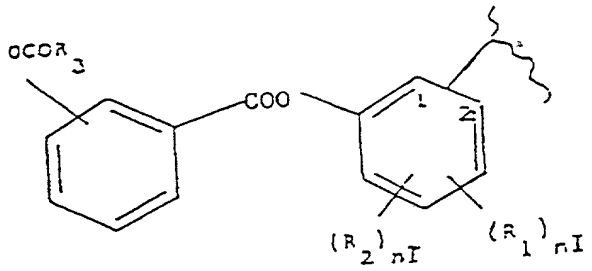
derivative obtained from (bromomethyl)phenol is still an unstable compound, which must be purified before reaction with the acid chloride. The (nitroxymethyl)phenol may further decompose in a not controllable way; consequently in order to obtain, on an industrial scale, the compound with the required purity for the final esterification step, the purification processes normally used in laboratory organic syntheses cannot be employed.

In conclusion the use of (nitroxymethyl)phenol in the synthesis of (nitroxymethyl)phenyl esters of aspirin derivatives is not industrially practicable.

It has been surprisingly and unexpectedly found by the Applicant that it is possible to synthetize (nitroxymethyl)phenyl esters of aspirin derivatives, and specifically (nitroxymethyl)phenyl esters of the N-acetylsalicylic acid, by synthetic reactions by which it can be avoided the use of the above mentioned phenol derivatives, and thus the purification steps of the intermediate compounds, obtaining the final products in good yields. Thus the new process is more advantageous than those of the prior art.

It is therefore an object of the present invention a new process for obtaining (nitroxymethyl)phenyl esters of aspirin derivatives of formula R-COOH wherein R is selected from one of the radicals having the following formula:





Ia) Ib)

wherein:

R_1 is the $OCOR_3$ group; wherein R_3 is methyl, ethyl or alkyl C_3-C_5, linear or branched, or the residue of a saturated heterocyclic ring having 5 or 6 atoms, containing hetero-atoms independently selected between O and N;

R_2 is hydrogen, halogen, C_1-C_4 alkyl, linear or branched when possible, C_1-C_4 alkoxyl, linear or branched when possible; C_1-C_4 perfluoroalkyl, linear or branched when possible, for example trifluoromethyl; nitro, mono- or di-(C_{1-4}) alkylamino;

R_1 and R_2 taken together are the dioxymethylene group, with the proviso in the formula Ib) that R_1 cannot be $OCOR_3$ in position 2 when R_3 is methyl;

nI is an integer and can have the values 0 or 1;

preferably in Ia) R_1 is acetoxy, preferably in ortho position with respect to the -CO- group, R_2 is hydrogen;

preferably in Ib) $R_3 = CH_3$, nI = 0;

preferably R-COOH is the acetylsalicylic acid;

said process comprising the following steps, generally carried

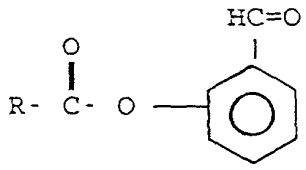
out in the presence of a solvent inert under the reaction conditions:

(1) reaction between the acid halide R-C(O)-X_I wherein:

X_I is an halogen selected between Cl and Br,

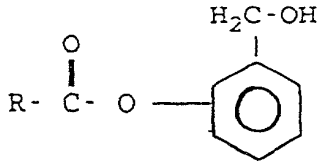
R is a radical as above defined,

in the presence of a base, with an isomer of the hydroxybenzaldehyde, i.e., wherein the hydroxyl group can be at ortho, meta or para position, with formation of a (carbonyl)phenyl ester (I):



(I)

(2) selective reduction of the aldehydic group of compound (I) with formation of an (hydroxymethyl)phenyl ester (II):



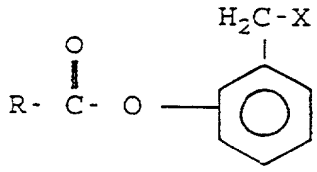
(II)

(3) reaction between the (hydroxymethyl) phenyl ester of formula (II) with:

a) SOX_2, X being an halogen selected between Cl and Br, with formation of an (halogenomethyl)phenyl ester of formula (III), wherein X = halogen,

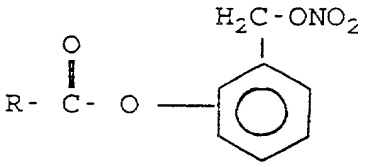
or

b) tosyl chloride or mesyl chloride with formation of a (tosyloxymethyl)- or (mesyloxymethyl)-phenylester, X being = O-tosyl or O-mesyl in formula (III):



(III)

(4) reaction between the compound of formula (III) with an inorganic nitrate salt, the metal cation of which belongs to the group IB or IIB, with formation of the corresponding (nitroxymethyl) phenyl ester



(IV)

The formation of the (carbonyl)phenyl ester of step (1) can alternatively be achieved by other reactions. For example by reaction of the aspirin derivative of general formula R-COOH with a dehydrating agent, such as for example N, N'-dicyclohexylcarbodiimide, in the presence of an aminopyridine derivative N, N disubstituted with alkyl radicals C_1-C_4 (step (1^I)), or with a C_1-C_4 alkylchloroformate in the presence of a base, soluble or insoluble in the reaction medium, as defined hereinafter (step (1^{II})), or with N, N' carbonyldiimidazol (step (1^{III})).

The process object of the present invention allows to obtain products at the required purity degree. Thus it is not necessary to purify the product compounds obtainable after each step. The overall yields are good (50-70%).

In step (1), the aspirin derivative acyl chloride or bromide, prepared from the corresponding compound in the acid form by using known reactants (ex. thionyl chloride, thionyl bromide, oxalyl chloride, oxalyl bromide, PCl_3, PBr_3), is let react in inert solvents (for example halogenated hydrocrbons such as dichloromethane, trichloromethane; ethers, such as ethyl ether, propyl ether, isopropyl ether, dioxane; esters such as ethyl acetate, propyl acetate, butyl acetate), in the presence of an organic or inorganic base, with an hydroxybenzaldehyde isomer as above defined. Said base can be soluble in the reaction solvent, as in the case of tertiary aliphatic amines of formula $N(R_N)_3$, wherein R_N is an alkyl group C_1-C_4, such as for example tributylamine, triethylamine, diethylmethylamine, trimethylamine; or said base can either be insoluble in the solvent, such as for example in the case of alkaline inorganic salts, for example, potassium carbonate, sodium carbonate, or alkaline metal bases such as NaOH and KOH.

When step 1) is substituted with step (1^I) as above defined, the aminopyridine derivative N, N disubstituted with alkyl radicals C_1-C_4, used in combination with the dehydrating

agent, is preferably selected for example from dimethylamino pyridine and dibutylamino pyridine; when instead step (1^{II}) is used, the compound C_1-C_4 alkylchloroformate is preferably selected between ethylchloroformate and isobutylchloroformate.

The reaction (2) of selective reduction of the aldehydic group to alcohol can be carried out by hydrogenation with gaseous hydrogen using conventional catalyts supported on carbon, such as for example, palladium, in a solution of the compound of formula (I) in an inert solvent. The reaction temperature is in the range 0-40°C, the gas pressure can range from 1 to 3 atm.

In alternative to the hydrogenation with gaseous hydrogen, reduction of compound (II) can be effected also with other reducing agents, for example inorganic mixed hydrides, such as for example $NaBH_4$, under the conditions well known to the skilled in the field.

Step (3) is carried out in an inert organic solvent at a temperature in the range 0°-40°C.

The alternative reaction between the alcohol and the tosyl chloride or mesyl chloride is carried out according to the known methods of the prior art.

Step (4) is carried out by adding an inorganic nitrate salt which cation is selected from metals belonging to the Groups IB and IIB, to a solution of the compound of formula (III), wherein X is halogen as above defined, or O-tosyl or O-

mesyl, in an organic solvent wherein said nitrate salt should be soluble, such as for example acetonitrile, tetrahydrofuran. The cation of the salt can be zinc, silver or mercury. Preferably the salt is silver nitrate. The reaction temperature can range between 20° and 90°C.

The synthesis appears to be specific:

when in the process object of the present invention are used as starting compounds other therapeutically active molecules having a reactive carboxylic function, it is found that the corresponding nitroxymethylphenyl esters are obtained with lower yields, as it is shown in the Examples.

The following Examples are given with the only purpose to illustrate the invention and they do not limit the same.

EXAMPLE 1

Preparation of the 2-(acetyloxy) benzoic acid 3-(nitroxymethyl)phenyl ester

EXAMPLE 1a

Preparation of the 2-(acetyloxy)benzoic acid 3-(formyl)phenyl ester

A mixture of 3-hydroxybenzaldehyde (830 g) and triethylamine (8.24 g) in methylene chloride (12.6 l) is kept under stirring, in inert nitrogen atmosphere, cooling at a temperature between -5°C and 0°C. Salicyloyl chloride (1650 g) is added in small portions in an hour. The mixture is still kept under stirring for 15 minutes, then water (10 l) is added and

the phases are separated. The aqueous phase is recovered and apart extracted with methylene chloride (3 l). The organic phases are joined together, washed with a 5% Na_2CO_3 solution (5 l X 2 times) and then with water (5 l X 2 times). The organic phase is dried with magnesium sulphate (2 Kg) in the presence of decolorating carbon (300 g). It is filtered under vacuum and the solvent is evaporated at reduced pressure at a bath temperature lower than 40°C, at last obtaining 1929 g of 3-(formyl)phenyl ester of the 2-(acetoxy) benzoic acid (quantitative yield) m.p. 80-84°C. The compound purity determined by HPLC, by using a LiChrospher® 100 RP 8 column, eluent buffer phosphate pH 8/acetonitrile 55/45, was equal to 98.5%.

EXAMPLE 1b

Preparation of the 2-(acetyloxy)benzoic acid 3-(hydroxy-methyl)phenyl ester

The 2-(acetyloxy)benzoic acid 3-(formyl)phenyl ester (1929 g) is dissolved in ethyl acetate (11 l) in the presence of 5% palladium on carbon (290 g) with the 50% of humidity.

The mixture is hydrogenated at room temperature and hydrogen pressure of about 2.5 atm, under stirring. The reaction during the first hour is slightly exothermic and the temperature in the reactor increases up to 35°C. After eight hours fresh catalyst (100 g) is added to complete the reaction. After 12 hours the reactor is discharged, the

catalyst is removed by filtration under vacuum, in nitrogen atmosphere, washing the panel with ethyl acetate (2 l). The organic phases are joined together and are washed with a 5% sodium bicarbonate solution (3 l X 2) and with water (3 l X 2). The organic phase is dried with magnesium sulphate (2 Kg) in the presence of decolorating carbon (100 g). It is filtered under vacuum and evaporated at reduced pressure at a bath temperature lower than 40°C, obtaining 1,850 g of 2-(acetyloxy)benzoic acid 3-(hydroxymethyl)phenyl ester with yield of 95.2%, m.p. 77-79°C. The compound purity determined by HPLC, by using a LiChrospher® 100 RP 8 column, eluent buffer phosphate pH 8/acetonitrile 55/45, is equal to 99.0%.

EXAMPLE 1c

Preparation of the 2-(acetyloxy)benzoic acid 3-(chloromethyl) phenyl ester

To a mixture consituted by 2-(acetyloxy)benzoic acid 3-(hydroxymethyl)phenyl ester (1850 g) and thionyl chloride (5.5 l) kept under stirring, dimethylformamide (5 ml) is added at room temperature and is left under stirring for one hour. At last the thionyl chloride is evaporated at reduced pressure at a bath temperature lower than 40°C. The residual traces of thionyl chloride in the compound are eliminated treating the solid with toluene (2 l X 2), which is then removed by evaporation at reduced pressure at a bath temperature lower than 40°C. The so obtained crude solid is

purified by crystallization with isopropyl ether (30 l), removing by filtration the residue which remains undissolved in the crystallization solvent brought to the boiling temperature.

After cooling and filtration at reduced pressure, a solid is isolated which is dried under vacuum at room temperature, obtaining 1,367 g (yield 69.4%) of 2-(acetyloxy)benzoic acid 3-(chloromethyl) phenyl ester m.p. 71-73°C. The compound purity, determined by HPLC using a LiChrospher® 100 RP 8 column, eluent buffer phosphate pH 8/acetonitrile 40/60, is 99.0%.

EXAMPLE 1d

Preparation of the 2-(acetyloxy)benzoic acid 3-(nitroxymethyl) phenyl ester

A solution of 2-(acetyloxy)benzoic acid 3-(chloromethyl) phenyl ester (1,367 g) in acetonitrile (8 l) is treated under stirring, sheltered from the light and at room temperature with $AgNO_3$ (915 g). It is heated up to reflux for two hours and then it is cooled at room temperature and $AgNO_3$ (115 g) is added. It is heated again at reflux and after 4 hours it is cooled to 10°C; the precipitate (silver salts) is filtered under vacuum and washed with acetonitrile (1 l X 2). The organic phases are joined together and the solvent evaporated under vacuum at a bath temperature lower than 40°C. The residue is dissolved in chloroform (4 l), decolorating carbon (100 g) is added, it is stirred and the organic phase is percolated

on a silica panel (2.5 Kg). The silica is washed with chloroform (10 l).

The organic phases are joined together and are concentrated to small volume at reduced pressure and bath temperature lower than 40°C until in the solution the formation of a precipitate (about 3 l by volume) is noticed. The volume of the solution is maintained constant by continuously feeding isopropyl ether (6 l), continuing the chloroform evaporation at reduced pressure until its complete removal from the organic phase. The organic phase is left under stirring for two hours at the temperature of 20°C. It is filtered under vacuum washing with isopropyl ether (1.5 l) the solid on the filter. After drying under vacuum at room temperature, 1200 g of 2-(acetyloxy)benzoic acid 3-(nitroxymethyl) phenyl ester (yield 80.7%) m.p. 63.5-64°C, are isolated. The compound purity, determined by HPLC by using a LiChrospher® 100 RP 8 column, eluent buffer phosphate pH 8/acetonitrile 50/50, is 99.75%. The final product structure has been confirmed by ^{1}H-NMR ($CDCl_3$): 8.22 (1H, dd), 7.66 (1H, td), 7.47 (1H, t), 7.40 (1H td), 7.32 (1H, d), 7.24-7.21 (2H, m), 7.18 (1H, dd), 5.44 (2H, s), 2.30 (3H, s).

The global process yield is 53.3%.

EXAMPLE 2

Preparation of the 2-(acetyloxy)benzoic acid 2-(nitroxymethyl)phenyl ester

The product is prepared acording to the procedure described in Example 1, by using as alcohol 2-hydroxybenzaldehyde. By analyzing the final compound obtained by chromatography on a thin layer of silica gel, using as eluent hexane/ethyl acetate 7/3, an unitary stain is obtained. The final product structure has been confirmed by ^{1}H-NMR ($CDCl_3$): 8.22 (1H, dd), 7.68 (1H, dt), 7.35 (6H, m), 5.40 (2H, s), 2.30 (3H, s). The global process yield is 67.8%.

EXAMPLE 3

Preparation of the 2-(acetyloxy)benzoic acid 4-(nitroxymethyl)phenyl ester

The product is prepared according to the procedure described in Example 1. The used aromatic hydroxy-aldehyde is 4-hydroxybenzaldehyde. By thin layer of silica gel, using as eluent hexane/ethyl acetate 7/3, an unitay stain is obtained. The final product structure has been confirmed by ^{1}H-NMR ($CDCl_3$): 8.21 (1H, dd), 7.66 (1H, dt), 7.42 (6H, m), 5.40 (2H, s), 2.25 (3H, s). The global process yield is 57.5%.

EXAMPLE 4

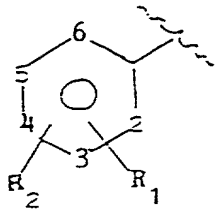
Preparation of the 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetic acid 3-(nitroxymethyl)phenyl ester

The product is prepared according to the procedure described in Example 1. The aromatic hydroxy-aldehyde used in step (1) is 3-hydroxybenzaldehyde. The global process yield is 39.1%. By analyzing the final product by chromatography on

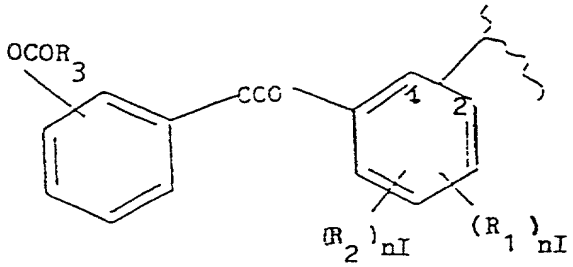
thin layer of silica gel, an unitary stain is obtained. M.p. 115-117°C. ^{1}H-NMR ($CDCl_3$): 7.70 (2H, d), 7.49 (2H, d), 7.42 (1H, t), 7.14-7.06 (4H, m), 6.90 (1H, d), 6.70 (1H, dd), 5.42 (2H, s), 3.93 (2H, s), 3.86 (3H, s) 2.48 (3H, s).

CLAIMS

1. A process for obtaining (nitroxymethyl)phenyl esters of aspirin derivatives of formula R-COOH wherein R is selected from one of the radicals having the following formula:



Ia)



Ib)

wherein:

R_1 is the $OCOR_3$ group; wherein R_3 is methyl, ethyl or alkyl C_3-C_5 linear or branched, or the residue of a saturated heterocyclic ring having 5 or 6 atoms, containing hetero-atoms independently selected between O and N;

R_2 is hydrogen, halogen, C_1-C_4 alkyl, linear or branched when possible, C_1-C_4 alkoxyl, linear or branched when possible; C_1-C_4 perfluoroalkyl, linear or branched when possible; nitro, mono- or di-(C_{1-4}) alkylamino;

R_1 and R_2 taken together are the dioxymethylene group, with the proviso that in the formula Ib) R_1 cannot be $OCOR_3$ in position 2 when R_3 is methyl;

nI is an integer and can take the values 0 or 1;

said synthesis process comprising the following steps:

(1) reaction between the halide R-C(O)-X_I (A) wherein: X_I is Cl, Br, R being a radical as above defined, with an isomer of the hydroxy-benzaldehyde, in the presence of a base, with formation of a (carbonyl)phenyl ester;

(2) reduction of aldehydic group of the (carbonyl)phenyl ester with formation of an (hydroxymethyl)phenyl ester;

(3) reaction between (hydroxymethyl) phenyl ester of formula (II) with:

a) SOX_2, X being an halogen selected between Cl and Br,

or

b) tosyl chloride or mesyl chloride ;

(4) reaction between the ester isolated at the previous step with an inorganic nitrate salt, which metal cation belongs to the group IB or IIB, with formation of the (nitroxymethyl) phenyl ester.

2. A process according to claim 1, wherein the formation of the (carbonyl)phenyl ester expected in step (1) is alternatively carried out by reacting the aspirin derivative of formula R-COOH with a dehydrating agent in the presence of an aminopyridine derivative N, N disubstituted with alkyl radicals C_1-C_4, or of a C_1-C_4

alkylchloroformate in the presence of a base, or with N, N' carbonyldiimidazole.

3. A process according to claim 1, wherein the nitrate used in step (4) is silver nitrate.

4. A process according to claims 1-3, wherein the aspirin derivative of formula R-COOH is the acetylsalicylic acid.

5. (Hydroxymethyl)phenyleter of aspirin derivatives of formula R-COOH, wherein R is as above defined in claim 1.

Docket No. _____

ARENT FOX KINTNER PLOTKIN & KAHN, PLLC
Nikaido, Marmelstein, Murray & Oram Intellectual Property Group

Declaration For U.S. Patent Application

As a below named inventor, I hereby declare that:
My residence, post office address and citizenship are as stated below my name.
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention **entitled**
(Insert Title) "SYNTHESIS METHOD OF NITROXYMETHYLPHENYL ESTERS OF ASPIRIN DERIVATIVES"
the specification of which is attached hereto unless the following box is checked:

☐ was filed on January 18, 2000 As PCT International Application
Number PCT/EP00/00353 and was amended on _____
And/or was filed on _____ As United States Application
Number _____ and was amended on _____

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claim(s), as amended by any amendment referred to above.
I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. §1.56.
I hereby claim foreign priority benefits under 35 U.S.C. §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate or PCT International Application having a filing date before that of the application(s) for which priority is claimed:

				Priority Claimed
(List prior foreign applications)	MI99A000134 (Number)	ITALY (Country)	26 January 1999 (Day/Month/Year Filed)	☒ Yes ☐ No
	_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	☐ Yes ☐ No
	_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	☐ Yes ☐ No

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

_____ (Application Number) _____ (Filing Date)
_____ (Application Number) _____ (Filing Date)

☐ See attached list for additional prior foreign or provisional applications.

I hereby claim the benefit under 35 U.S.C. §120 of any United States application(s) or §365(c) of any PCT International application(s) designating the United States of America listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior application(s) (U.S. or PCT) in the manner provided by the first paragraph of 35, U.S.C. §112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. §1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

(List prior U.S. Applications or PCT International applications designating the U.S.)			
	_____ (Application Serial No.)	_____ (Filing Date)	_____ (Status) (patented, pending, abandoned)
	_____ (Application Serial No.)	_____ (Filing Date)	_____ (Status) (patented, pending, abandoned)

14 And I hereby appoint the firm of Arent Fox, Customer Number 004372 including as principal attorneys: Robert B. Murray, Reg. No. 22,980; Charles M. Marmelstein, Reg. No. 25,895; George E. Oram, Jr., Reg. No. 27,931; Douglas H. Goldhush, Reg. No. 33,125; David T. Nikaido, Reg. No. 22,663; Richard J. Berman, Reg. No. 39,107; Murat Ozgu, Reg. No. 44,275; Robert K. Carpenter, Reg. No. 34,794; Gregory B. Kang, Reg. No. 45,273; Rustan Hill, Reg. No. 37,351; Kevin Turner, Reg. No. 43,437; Carl Schaukowitch, Reg. No. 29,211; Hans J. Crosby, Reg. No. 44,634, and Brian A. Tollefson, Reg. No. 46,338.

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The undersigned hereby authorizes the U.S. attorneys named herein to accept and follow instructions from the undersigned's assignee, if any, and/or, if the undersigned is not a resident of the United States, the undersigned's domestic attorney, patent attorney or patent agent, as to any action to be take in the Patent and Trademark Office regarding this application without direct communication between the U.S. attorneys and the undersigned. In the event of a change in the person(s) from whom instructions may be taken, the U.S. attorneys named herein will be so notified by the undersigned.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1.00

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